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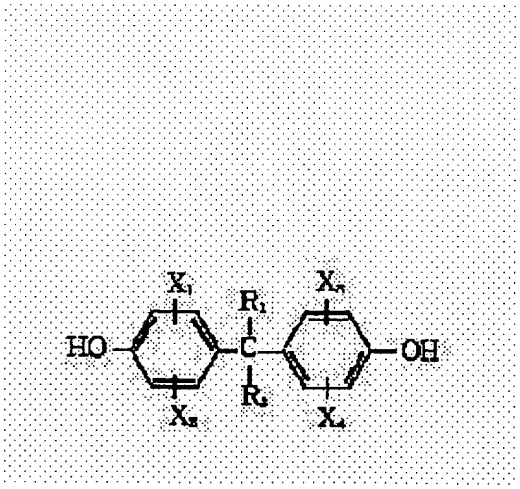
(54) THROMBOLYSIS ACCELERATOR CONTAINING DIPHENYL HYDROCARBON DERIVATIVE AS ACTIVE COMPONENT

(57)Abstract:

PURPOSE: To provide the subject agent containing a specific compound as an active component, having excellent thrombolytic activity, enabling peroral administration, stably retained in the living body and capable of effectively inhibiting the inactivation of plasmin by a α2-plasmin inhibitor.

CONSTITUTION: The objective agent contains a diphenyl hydrocarbon derivative of formula (R1 and R2



are H or 1-10C chain alkyl; X1 to X4 are H, amino, etc., provided that X1 to X4 are not H at the same time) {e.g. 4-[1-(4- hydroxyphenyl)-1,3-dimethylbutylidene]-pyrocatechol} as an active component. The compound of formula can be produced by dissolving a phenol derivative of formula (all the groups X1 to Xa are H) in methylene chloride and dropping aqueous solution of nitric acid at 10-15°C to effect the nitration of the compound. The compounds of formula wherein R1 is 1-10C straight-chain alkyl or 3-10C branched-chain alkyl and R2 is 3-10C branched-chain alkyl are new compounds.

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* NOTICES *

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2.**** shows the word which can not be translated.
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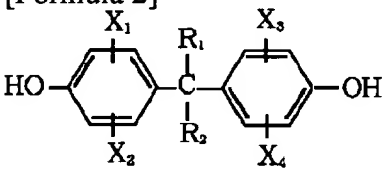
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to use of a diphenyl hydrocarbon derivative and its drugs. It is related with the thrombolysis accelerator which contains the diphenyl hydrocarbon derivative which has the inhibitory action of the alpha2-plasmin inhibitor (it abbreviates to alpha2-PI below) which plays a still more detailed role important for deactivation of plasmin as an active principle.
[0002]
[Description of the Prior Art] The research for establishment of the cause therapy of various adult diseases is progressing quickly with extension of global average life. The cerebral apoplexy and myocardial infarction which produce local blood coagulation in the parts of a blood vessel in the living body, the heart, etc. are also one for [the / main] research. Conventionally, heparin is one of those typical which are used as anticoagulant. this -- anti -- fatty tuna -- it acts on Bottle III and it is supposed that an operation of a thrombin is suppressed and blood coagulation is stopped. Moreover, although dextran sulfate reinforces antithrombin III activity like heparin, activity control of antiplasmin is reported [Aoki, clinical [of dextran sulfate], 1979, 65 pages, and a medical-affairs publishing company]. In addition, it is known that platelet aggregation inhibitors, such as aspirin and ticlopidine, will also be used as a vantithrombotic. However, these drugs do not mainly control thrombosis and are not useful to the dissolution of a thrombus.
[0003] Urokinase (it omits Following UK) and streptokinase (it omits Following SK) are used for the dissolution of a thrombus from the former. These change the plasminogen in blood into active plasmin, dissolve a thrombus, and are especially confirmed in early stages of formation of a thrombus. Recently, it is prosperous in the research which uses human plasminogen AKUCHI **-TA - (it omits Following tPA). However, since these thrombolytic agents are protein pharmaceutical preparation, they are difficult to administer orally, and moreover, its half-life in blood is very short.
[0004] It could administer orally from such a background, and existed in stability in the living body, and an appearance of drugs with the solvent action of a thrombus was desired. There are many examples which tried thrombolysis with the synthetic compound before this invention. For example, KN.von [Proc.Soc.Exp.Biol.Med.106,530 (1961)] R.J.Gryglewski and others has reported the thrombolysis operation of flufenamic acid for the example for which Kaulla and others used benzoic acids [Nature, 214,626 (1967)]. However, the report which suggests these thrombolysis operations has inadequate activity, or there is much what has the not clear mechanism of action. Moreover, the many are in. There is almost nothing that reports the enzyme chemical result of vitro and reports effectiveness in the thrombus model using an animal.
[0005] By the way, thrombolysis is that the fibrin lump in a thrombus is disassembled by plasmin. plasmin -- the inside of blood -- as plasminogen -- existing -- various AKUCHI, such as UK, SK, and tPA, -- it activates more better and becomes plasmin. Although the generated plasmin disassembles a fibrin lump, it is inactivated by the various inhibitor which exists in blood. It is called alpha2-PI to have played the role most important for deactivation of plasmin. alpha2-PI exists 1/3 mol of abbreviation of

plasminogen in blood. Therefore, if a lot of activators are not prescribed for the patient, plasmin effective in fibrin lump decomposition cannot be made to generate in the case of the fibrinolytic therapy which prescribes an activator for the patient from the exterior.
[0006]
[Problem(s) to be Solved by the Invention] this invention persons made the amount of effective plasmins increase, when checking inactivation of the plasmin by alpha2-PI, and I thought that fibrin decomposition could be attained efficiently. According to the report of Aoki and others, an alpha2-PI defective is in a bleeding tendency by fibrinogenolysis ability sthenia, and alpha2-PI level has a report that it is intentionally high [internal medicine, 51 volumes, 82 pages, and 1983]. It has suggested that these reports can activate a fibrinolytic system by controlling an operation of alpha2-PI.
[0007] Therefore, the purpose of this invention is offering the thrombolysis accelerator which can check inactivation of the plasmin by alpha2-PI effectively. Other purposes of this invention are offering the thrombolysis accelerator which contains a synthetic compound as an active principle. Furthermore, other purposes of this invention are offering the thrombolysis accelerator in which could administer orally, and existed in stability in the living body, and thrombolysis ability's was excellent.
[0008]
[Means for Solving the Problem] the purpose of above-mentioned this invention -- a general formula -- (1 [-izing 2])
[0009]
[Formula 2]



(1)

(The shape of a straight chain and branched-chain alkyl group of hydrogen or carbon numbers 1-10 is independently shown by the inside R1 and R2 of a formula.) X1, X2, X3, and X4 show hydrogen or a low-grade alkyl group, a nitro group, the amino group, an acetamide radical, hydroxyl, a low-grade alkanoyl radical, a hydroxymethyl group, a halogen atom, a lower alkoxy group, a carboxyl group, benzoyl, and an aryl group independently. However, X1, X2, X3, and X4 remove to coincidence the case where it is hydrogen. It is attained by the thrombolysis accelerator which contains the salt permitted on the diphenyl hydrocarbon derivative expressed and its therapy as an active principle.
[0010] As for a diphenyl hydrocarbon derivative, many derivatives are already compounded as a plastics raw material, and the chemical property is known well. However, a thrombolysis operation of these compounds is not reported at all. Activating a fibrinolytic system without these compounds' showing anti-alpha2-PI activity, and participating in a coagulation system, also in various thrombosis symptoms models, the effective fact will not be found out without this invention person etc., and will offer the epoch-making cure based on a new operation concept.
[0011] With the shape of a straight chain of the carbon numbers 1-10 in this invention, and a branched-chain alkyl group A methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, 1-methylbutyl radical, 2-methylbutyl radical, a neopentyl radical, a hexyl group, An iso hexyl group, 1-methyl hexyl group, 3-methyl hexyl group, 5-methyl hexyl group, Heptyl radical, 4, and 4-dimethyl pentyl radical, 6-methyl PEPUCHIRU radical, 7-methyl octyl radical, an octyl radical, 8-methyl nonyl radical, a deca nil radical, etc. are shown. With a low-grade alkyl group A methyl group, an ethyl group, a propyl group, butyl, etc. are shown. With a low-grade alkanoyl radical An acetyl group, a propionyl radical, a butyryl radical, or an isobutyryl radical is shown, a halogen atom shows a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom, and a lower alkoxy group shows a methoxy group, an ethoxy radical, a butoxy radical, etc.
[0012] The inside R1 of the compound expressed with a general formula (1) by the straight chain-like

alkyl group of carbon numbers 1-10 The diphenyl hydrocarbon derivative whose R2 is the branched-chain alkyl group of carbon numbers 3-10 however, a 2 and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane -- A 2 and 2-screw [4-hydroxy-3-(1-methylethyl) phenyl]-4-methyl pentane, A 2 and 2-screw [4-hydroxy-3-(1 and 1-dimethyl ethyl) phenyl]-4-methyl pentane, A 2 and 2-bis(3, 5-diethyl-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(4-hydroxy-3-methoxypheny)-4-methyl pentane, the case of the 2 and 2-bis(4-hydroxy-3-methylphenyl)-3-methyl pentane, 2, and 2-screw (4-hydroxy-3-methylphenyl) -3 and 3-dimethyl butane -- removing -- it is a new molecular entity and this invention also contains these. With the straight chain-like alkyl group of the carbon numbers 1-10 currently mentioned here A methyl group, an ethyl group, a propyl group, butyl, a pentyl radical, a hexyl group, an octyl radical, a nonyl radical, a deca nil radical, etc. are shown. With the branched-chain alkyl group of carbon numbers 3-10 An isopropyl group, an isobutyl radical, sec-butyl, tert-butyl, An isopentyl radical, 1-methylbutyl radical, 2-methylbutyl radical, a neopentyl radical, Iso hexyl group, 1-methyl hexyl group, 3-methyl hexyl group, 5-methyl hexyl group, 4, and 4-dimethyl pentyl radical, 6-methyl heptyl radical, 7-methyl octyl radical, 8-methyl nonyl radical, etc. are shown. It is a new molecular entity and, as for the diphenyl hydrocarbon derivative (however, the case of the 3 and 3-screw (3, 4-dihydroxy phenyl) -2 and 4-dimethyl pentane is removed) whose inside R1 and R2 of the compound furthermore expressed with a general formula (1) is the branched-chain alkyl of carbon numbers 3-10 independently, these also contain this invention. The branched-chain alkyl group of the carbon numbers 3-10 currently mentioned here is the same semantics as the above.

[0013] It is as follows when these compounds are illustrated concretely. A bis(4-hydroxy-3-methylphenyl) methane, 2, and 2-bis(4-hydroxy-3-methylphenyl) propane, 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-3-methyl phenol, 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-2-methyl phenol, 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-2, 6-dimethylphenol, A 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-3-(1-methylethyl) phenol, A 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-2-nitrophenol, A 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-2-aminophenol, A 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-pyrocatechol, A 3-[1-(4-hydroxyphenyl)-1-methylethylidene]-6-hydroxybenzoic acid, 3-[1-(4-hydroxyphenyl)-1-methylethylidene]-6-benzyl alcohol, A 2 and 2-bis(3-carboxy-4-hydroxyphenyl) propane, A 2 and 2-bis(3-acetylamino-4-hydroxyphenyl) propane, A 2 and 2-bis(3-acetyl-4-hydroxyphenyl) propane, A 2 and 2-bis[4-hydroxy-3-(2-propenyl) phenyl] propane, A 2 and 2-bis(3-benzoyl-4-hydroxyphenyl) propane, RU 4-[1-(4-hydroxyphenyl)-1-methylethylidene] - 1, 2, and 6-benzene trio - 2 and 2-bis(4-hydroxy-3-methylphenyl) butane, 2, and 2-bis(3, 5-dimethyl-4-hydroxyphenyl) butane, A 2 and 2-bis(4-hydroxy-3-nitrophenyl) butane, 3, and 3-bis(4-hydroxy-3-methylphenyl) pentane, A 3 and 3-bis(4-hydroxy-3-nitrophenyl) pentane, 3, and 3-bis(3-amino-4-hydroxyphenyl) pentane, A 3 and 3-bis(3-acetylamino-4-hydroxyphenyl) pentane, A 2 and 2-bis(3, 4-dihydroxy phenyl) pentane, a 4-[1-(4-hydroxyphenyl)-1-methyl butylidene]-pyrocatechol, A 2 and 2-bis (3, 5-diethyl-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane, A 2 and 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(4-hydroxy-3-methoxypheny)-4-methyl pentane, A 2 and 2-screw [3-(1-methylethyl)-4-hydroxyphenyl]-4-methyl pentane, A 2 and 2-screw [3-(1 and 1-dimethyl ethyl)-4-hydroxyphenyl]-4-methyl pentane, A 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-2-nitrophenol, A 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-2-aminophenol, A 2 and 2-bis(4-hydroxy-3-nitrophenyl)-4-methyl pentane, A 2 and 2-bis(3-amino-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(3-acetylamino-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(3-carboxy-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(3, 4-dihydroxy phenyl)-4-methyl pentane, A 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-pyrocatechol, A 2 and 2-bis(3-hydroxymethyl-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(3-acetyl-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-bis(3-benzoyl-4-hydroxyphenyl)-4-methyl pentane, A 2 and 2-screw [4-hydroxy-3-(2-propenyl) phenyl]-4-methyl pentane, 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-3-methyl phenol, 2 and 2-bis(4-hydroxy-3-nitrophenyl)-3-methyl butane, A 3-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-6-hydroxy acetophenone, The 2 and 2-bis(4-hydroxy-3-methylphenyl) hexane 2, a 2-bis(3-ethyl-4-hydroxyphenyl) hexane, A 3 and 3-

bis(4-hydroxy-3-nitrophenyl)-5-methyl hexane, 2 and 2-bis(3-carboxy-4-hydroxyphenyl)-4-methylheptane, RU 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene] - 1, 2, and 6-benzene trio - A 5 and 5-bis(3, 5-dimethyl-4-hydroxyphenyl) nonane, RU 5 and 5-bis(4-hydroxy-3-nitrophenyl) nonane and 4-[1-(4-hydroxyphenyl)-1-butyl pen dust DIN] - 1, 2, and 5-benzene trio - A 5 and 5-bis(4-hydroxy-3-methylphenyl) Deccan, 5, and 5-bis(4-hydroxy-3-methylphenyl) tridecane, The 3 and 3-screw (3, 4-dihydroxy phenyl) -2, 4-dimethyl pentane, The 3 and 3-screw (4-hydroxy-3-nitrophenyl) -2, 5-dimethyl hexane, 2 and 2-screw (4-hydroxy-3-methylphenyl) -3, 3-dimethyl butane, 2, and 2-bis(4-hydroxy-3-methylphenyl)-3-methyl pentane, 4, and 4-screw (3-acetyl-4-hydroxyphenyl) - 2 Six - A dimethyl heptane, 4, and 4-bis(4-hydroxy-3-nitrophenyl) octane, The 5 and 5-screw (3, 5-dimethyl-4-hydroxyphenyl) -2, 8-dimethyl nonane 4, 4-screw (3-ethyl-4-hydroxyphenyl) - 2, 2, a 7-trimethyl octane, The 6 and 6-screw (3-ethyl-4-hydroxyphenyl) -2, 10-dimethyl undecane, 7, 7-screw [3-(1 and 1-dimethyl ethyl)-4-hydroxyphenyl]-2, and 12-dimethyl tridecane, 7, 7-screw [4-hydroxy-3-(2-propenyl) phenyl]-3, 11-dimethyl tridecane, The 7 and 7-screw (3-BUROMO-4-hydroxyphenyl) -5, 9-dimethyl tridecane, 6 and 6-screw (4-hydroxy-3-nitrophenyl) - 2, 2, 11-trimethyl dodecane, 6, and 6-screw (3-BUROMO-4-hydroxyphenyl) - 2, 2, and 12-trimethyl tridecane ** etc. is mentioned.

[0014] The phenol derivative expressed with the general formula (1) in this invention is compoundable by the approach shown below.

a) In nitration and an amination general formula (1), X1, X2, X3, and X4 melt at coincidence the phenol derivative which is hydrogen to solvents, such as a methylene chloride, chloroform, and 1,2-dichloroethane, and a nitro object is easily compoundable by dropping nitric-acid water 25 - 30%, keeping a reaction solution at 10-15 degrees C. The number of the substituents introduced in this reaction can be controlled by reaction time, and composition of a mono-nitroglycerine object, a dinitro object, a trinitro object, etc. is possible for it. It can lead to the amino object which corresponds easily by performing the acquired nitro object under 10% palladium carbon existence, and performing hydrogenation in solvents, such as a methanol and ethanol.

[0015] b) A hydroxyl object is easily compoundable by X1, X2, X3, and X4 melting at coincidence the phenol derivative which is hydrogen to an acetic acid or a hydrochloric acid in a hydroxylation general formula (1), and carrying out the short-time reaction of the hydrochloric-acid water solution of sodium metaperiodate at a room temperature.

[0016] c) When X1, X2, X3, and X4 make halogenating agents, such as a bromine, the phenol derivative which is hydrogen react to coincidence at a 1 - four-mol room temperature among hypochlorous-acid t-butyl or an acetic acid among a carbon tetrachloride in a halogenation general formula (1), the Krol object and a bromine object are easily compoundable.

[0017] d) After protecting the hydroxyl group of the phenol derivative X1, X2, X3, and whose X4 are hydrogen in an acylation general formula (1) at coincidence by alkyl groups, such as a methyl group and an ethyl group, the acetyl object and benzoyl object which correspond easily are compoundable by making 1-4 mols react at 50-70 degrees C under existence of an aluminum chloride using acylating agents, such as an acetyl chloride and a benzoyl chloride, in solvents, such as a methylene chloride, chloroform, and 1,2-dichloroethane.

[0018] e) In carboxylation and a carboxymethyl-ized general formula (1), X1, X2, X3, and X4 protect to coincidence the hydroxyl group of the phenol derivative which is hydrogen by the methoxymethyl radical, and make it react among solvents, such as the ether and a tetrahydro furan, with n-butyl lithium of 2 equivalence - 4 equivalence in -40--50 degree C. If the generated lithium salt is made to react with superfluous dry ice and deprotection of the protective group of a hydroxyl group is carried out, the carboxyl object which corresponds easily can be acquired. Moreover, if the acquired carboxyl object is made to react with the lithium hydride aluminum in a tetrahydro furan, it can lead to the carboxymethyl object which corresponds easily.

[0019] The compound of this invention has the outstanding thrombolysis operation, and is effective in prevention or the therapy of various kinds of illnesses accompanied by formation of a fibrin blood clot, such as cerebrovascular disease, such as ischemic heart disease, such as chronic arteriosclerosis, such as arteriosclerosis obliterans, Buerger disease, peripheral arteriosclerosis, and a Raynaud's disease,

pulmonary embolism, angina pectoris, myocardial infarction, and coronary occlusion, TIA (transient ischemic attack), cerebral infarction (a thrombus, plug), and cerebral arteriosclerosis. To UK, SK, and tPA being used for the thrombolytic therapy of an acute stage, the compound of this invention can be administered orally, and since it exists in stability in the living body, it is applicable to recurrence prevention of ischemic heart diseases, such as a chronic therapy, myocardial infarction, etc. of thrombosis. Although the effectiveness as a thrombolytic agent is shown even when the compound of this invention is independent so that the pharmacology research result shown in the below-mentioned example may show, it can be used also for the purpose which it uses [purpose] together with UK, SK, and tPA, and reinforces the operation.

[0020] When using the compound of this invention as a thrombolytic agent, naturally the dose and dosage forms change with the physical properties of a compound, symptoms for administration, etc., but when prescribing a medicine for the patient in taking orally, 1-1000mg per adult day is divided into 2 - 4 times, and it can be used as a tablet, a granule, powder, suspension, a capsule, etc. Moreover, when prescribing a medicine for the patient parenterally, 1-500mg per adult day is divided into 2 - 4 times, for example, a medicine can be prescribed for the patient as injections, suppositories, and an isotonic solution for infusion solutions. What is necessary is just to perform pharmaceutical preparation-ization according to a well-known approach. for example, the case where it considers as a tablet -- as an excipient -- corn starch, a lactose, calcium phosphate, magnesium stearate, etc., as a binder, starch, an agar, a calcium carbonate, etc. are used as disintegrator, and a hydroxyl propyl cellulose, carboxyl methyl cellulose, gum arabic, etc. are used for magnesium stearate, talc, etc. as lubricant. These tablets are not hindered by coating suitably according to glycocalyx, gelatin clothes, and other need. Moreover, when considering as injections, it is possible the nonaqueous nature solution using cotton seed oil, corn oil, peanut oil, and olive oil and to add water to the compound of this invention further, and to use it as suspension or an emulsion for the bottom of existence of a suitable surfactant. Although especially a limit does not have the content of the active principle in pharmaceutical preparation, solid-state pharmaceutical preparation and liquid pharmaceutical preparation are usually 1 - 90%.

[0021]

[Example] Although an example explains this invention below, this invention is not limited to these examples.

Example 12 of manufacture, 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane 2, and 2-bis(4-hydroxyphenyl)-4-methyl pentane 2.2g was dissolved in 10ml of carbon tetrachlorides, and 2ml of bottom hypochlorous-acid of cooling t-butyl 1.9ml carbon-tetrachloride solutions was dropped. 1 hour after, vacuum concentration of the solvent was carried out and silica gel column chromatography refined concentration residue. A methanol/chloroform = when 1/50 refined, pure 2 and 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane 1.1g was obtained as yellow oily matter.

IR nu cm-1(neat):3528, 1607, 1499, 1407, 1337, 1286 and 1185, 875NMR delta ppm (CDCl3) : [0.74 (d, 6H),] 1.48 (m, 1H), 1.57 (s, 3H), 1.95 (d, 2H), 5.44 (s, 2H), 6.90 (d, 2H), 6.96 (dd, 2H), 7.14 (d, 2H)

[0022] 8ml of concentrated hydrochloric acid was added to mixed liquor (example 22 of manufacture, and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane o-cresol 21.6g, and methyl-isobutyl-ketone 5.0g), hydrochloric acid gas was saturated, and it stirred for seven days at the room temperature. After adding water to reaction mixture and carrying out azeotropy distilling off of the phenol, benzene was added and azeotropy distilling off of the water was carried out. Silica gel column chromatography refined the obtained concentration residue. When eluted with chloroform, pure 2 and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane 3.8g was obtained as a colorless solid-state.

m. p.:126-128-degree-CIR nu cm-1(KBr):3354, 1611, 1508, 1461, 1412, 1346 and 1295, 1253NMR delta ppm (CDCl3) : [0.73 (d, 6H),] 1, 47 (m, 1H), 1.57 (s, 3H), 1.96 (d, 2H), 2.20 (s, 6H), 4.61 (s, 2H), 6.61 (d, 2H), 6.87 (dd, 2H), 6.93 (d, 2H)

[0023] Example of manufacture 34-[1-(4-hydroxyphenyl)-1-methylethylidene]-3-(1-methylethyl) phenol isopropenyl phenol 2.9g and m-isopropyl phenol 8.9g were melted to chloroform 20ml, and p-toluenesulfonic acid was stirred at catalyst ****** and a room temperature for 48 hours. Vacuum

concentration of the solvent was carried out and silica gel column chromatography refined concentration residue. Ethyl acetate / n-hexane = when eluted in 1/15, pure 4-[1-(4-hydroxyphenyl)-1-methylethylidene]-3-(1-methylethyl) phenol 1.5g was obtained as a colorless solid-state.
m. p.:107-109-degree-CIR nu cm-1(KBr):3369, 1613, 1587, 1565, 1512, 1430 and 1361, 1298NMR delta ppm (CDCl3) : [1.22 (d, 6H),] 1.62 (s, 6H), 2.83 (q, 1H), 4.48 (s, 1H), 5.10 (s, 1H), 6.62 (s, 1H), 6.74 (d, 2H), 7.19 (d, 2H), 6.81 (d, 1H), 7.33 (d, 1H)
[0024] Example 14-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-2-nitrophenol 2 and 2-bis(4-hydroxyphenyl)-4-methyl pentane 3.8g was dissolved in 1,2-dichloroethane 76ml, and nitric-acid water was dropped slowly 30%, keeping reaction temperature at 10-15 degrees C. It checked that the color of a reaction solution changed to dark reddish-brown from yellow, and the reaction was advancing by thin layer chromatography, and water was added, the reaction was suspended, chloroform extracted, and it dried with the sodium sulfate. Vacuum concentration of the solvent was carried out and silica gel column chromatography refined residue. A methanol/chloroform = when elution was carried out with 1/50 of mixed solvents, pure 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-2-nitrophenol 2.6g was obtained as yellow oily matter.
IR nucm -1 (neat):3398, 1629, 1536, 1513, 1418, 1181 and 1081, 832NMR deltappm (CDCl3) : [0.75 (d, 6H),] 1.50 (m, 1H) and 1.62 (s, 3H) -- 2.01 (d, 2H), 4.76 (br, 1H), 6.74 (d, 2H) 7.02 (d, 1H), and 7.02 (dd, 2H) and 7.30 (dd, 1H) -- 8.04 (d, 1H) and 10.53 (s, 1H)
[0025] Example 22, 2-bis(4-hydroxy-3-nitrophenyl)-4-methyl pentane 2, and 2-bis(4-hydroxyphenyl)-4-methyl pentane 3.8g was dissolved in 1,2-dichloroethane 40ml, and nitric-acid water was dropped slowly 30%, keeping reaction temperature at 10-15 degrees C. After checking raw material disappearance, water was added, the reaction was suspended, chloroform extracted and it dried with the sodium sulfate. Vacuum concentration of the solvent was carried out and silica gel column chromatography refined residue. Chloroform/hexane = when elution was carried out with 4/1 of mixed solvents, pure 2 and 2-bis(4-hydroxy-3-nitrophenyl)-4-methyl pentane 4.5g was obtained as yellow oily matter.
IR nucm -1 (neat):3256, 1629, 1583, 1420, 1323, 899 and 837, 765NMR deltappm (CDCl3) : 0.78 (d, 6H), 1.50 (m, 1H), 1.67 (s, 3H), 2.05 (d, 2H), 7.06 (d, 2H), 7.28 (dd, 2H) 8.03 (d, 2H), 10.54 (s, 2H)
[0026] an example -- 34 - [-- one - (4-hydroxyphenyl) - one -- three - dimethyl -- butylidene --] - a pyrocatechol -- four - [-- one - (4-hydroxyphenyl) - one -- three - dimethyl -- butylidene --] - two - an aminophenol -- one -- g -- an acetic acid -- a solution -- 300 -- ml -- sodium metaperiodate -- ten -- g -- dissolving -- having made -- 0.1 -- N -- a hydrochloric acid -- water -- 700 -- ml -- 3.5 -- a minute -- applying -- having been dropped . After the reaction solution changed from colorlessness to red, chloroform 400ml was added and extracted. The organic layer was washed with water, 3g of potassium iodide and 200ml of acetic acids were added, and it stirred for 2 minutes. 100ml of sodium hydrogensulfites washed this solution 5%. Vacuum concentration of the solvent was carried out after desiccation with the sodium sulfate, and silica column chromatography refined concentration residue. A methanol/chloroform = when eluted with 1/10 of mixed solvents, pure 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-pyrocatechol 0.98g was obtained as yellow oily matter.
IR nu cm-1(neat):3359, 1700, 1611, 1512, 1434, 1110 and 1014, 938NMR delta ppm (CDCl3) : [0.69 (d, 6H),] 1.45 (m, 1H) and 1.47 (s, 3H) -- 1.87 (d, 2H), 6.45 (dd, 1H), 6.48 (d, 1H) 6.59 (d, 1H), and 6.62 (d, 2H) and 6.94 (d, 2H) -- 8.57 (s, 2H) and 9.09 (s, 1H)
[0027] 300ml of example 42, 2-bis(3, 4-dihydroxy phenyl)-4-methyl pentane 2, and 2-bis(3-amino-4-hydroxyphenyl)-4-methyl pentane 1g acetic-acid solutions was dropped at 700ml of 0.1-N hydrochloric-acid water in which 10g of sodium metaperiodate was dissolved. After the reaction solution changed from colorlessness to red, chloroform 400ml was added and extracted. The organic layer was washed with water, 3g of potassium iodide and 200ml of acetic acids were added, and it stirred for 2 minutes. 100ml of sodium-hydrogensulfite water solutions washed this solution 5%. Vacuum concentration of the solvent was carried out after desiccation with the sodium sulfate, and silica gel column chromatography refined residue. Chloroform/methanol = when elution was carried out with 10/1 of mixed solvents, pure 2 and 2-bis(3, 4-dihydroxy phenyl)-4-methyl pentane 0.83g was obtained as green oily matter.

IR nu cm-1(neat):3254, 1604, 1518, 1434, 1374, 1282 and 1206, 1122NMR delta ppm (DMSO-d6) : [0.69 (d, 6H),] 1.44 (s, 3H), 1.46 (m, 1H), 1.83 (d, 2H), 6.45 (m, 4H), 6.49 (d, 2H), 8.53 (s, 2H) 8.59 (s, 2H)

[0028] An example 52 and 17.6g of 2-bis(3-acetyl-4-hydroxyphenyl)-4-methyl pentane aluminum chlorides were suspended in 1,2-dichloroethane 70ml, and 8.9ml of acetyl chlorides was slowly dropped at 0 degree C. 2 and 2-bis(4-methoxypheny)-4-methyl pentane 5.4g was dropped at 0 degree C into this solution, and heating stirring was carried out at 70 degrees C for 1.5 hours. After it opened the reaction solution in iced water and the methylene chloride extracted, the organic layer was dried with the sodium sulfate. Vacuum concentration of the solvent was carried out and silica gel column chromatography refined residue. Ethyl acetate/hexane = when elution was carried out with 1/10 of mixed solvents, pure 2 and 2-bis(3-acetyl-4-hydroxyphenyl)-4-methyl pentane 2.85g was obtained as a yellow crystal.
m. p.:119-121-degree-CIR nu cm-1(KBr):3336, 1641, 1483, 1426, 1364, 1327 and 1299, 963NMR delta ppm(CDCl3):0.80 (d, 6H), 1.53 (m, 1H), 1.65 (s, 3H) 2.01 (d, 2H), and 2.59 (s, 6H) and 6.89 (d, 2H) -- 7.26 (dd, 2H) and 7.57 (d, 2H)

[0029] Example 62, 2-bis(3-carboxy-4-hydroxyphenyl)-4-methyl pentane 2, and 2-bis(4-methoxymethyl phenyl)-4-methyl pentane 2.0g was dissolved in ether 20ml. This solution was cooled at -40--50 degree C, 14ml of 1.6 M-n-butyl lithium hexane solutions was dropped, and reaction temperature was returned to the room temperature and stirred for 2 hours. Dry ice (about 10g) was added to this reaction solution, and it stirred at the room temperature for 1 hour. After adding water and suspending a reaction, the ether extracted by having made the water layer into hydrochloric-acid acidity, and silica gel column chromatography refined concentration residue. A methanol/chloroform = when elution was carried out with 1/40 of mixed solvents, pure 2 and 2-bis(3-carboxy-4-methoxymethyl phenyl)-4-methyl pentane 1.2g was obtained as oily matter. Obtained 2 and 2-bis(3-carboxy-4-methoxymethyl phenyl)-4-methyl pentane 1.2g was dissolved in methanol 30ml, 12ml of 3-N hydrochloric-acid water solutions was added, and it stirred at the room temperature overnight. When benzene is added to the residue which carried out vacuum concentration of the reaction mixture, and obtained it and it was crystallized, pure 2 and 2-bis(3-carboxy-4-hydroxyphenyl)-4-methyl pentane 0.74g was obtained as a colorless crystal.
m. p.227-228-degree-CIR nu cm-1(KBr):3447, 1670, 1490, 1446, 1296, 1213 831 NMR delta ppm (DMS0-d6):0.71 (d, 6H), 1.44 (m, 1H), 1.56 (s, 3H) 1.97 (d, 2H), and 6.85 (d, 2H) and 7.15 (br, 2H) -- 7.25 (d, 2H) and 7.63 (d, 2H)

[0030] Example 72, tablet [which makes an active principle a 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane] 2, and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane 50g, 38g [of lactoses], and corn starch 35g, and 20g of crystalline cellulose are often mixed, kneading granulation of this is carried out with the liquid which dissolved hydroxypropylcellulose 5g in water, and it dries at 50 degrees C for 4 hours. 2g of magnesium stearates could be added to this, and it mixed, and tableted by the weight of 150mg per one lock using the tableting machine, and the tablet was obtained.

[0031] Example 82, capsule [which makes an active principle a 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane] 2, and 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane 100g, 70g [of lactoses], and corn starch 70g, 40g of crystalline cellulose, and 6g of magnesium stearates are often mixed. This was addressing[to 300mg]-filled up with the encapsulation machine into the hard filled capsule, and the capsule was obtained.

[0032] It is easy to take example 92, granule [which makes an active principle a 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane] 2, and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane 100g, 150g [of lactoses], and corn starch 140g, and 80g of crystalline cellulose, and mixes, kneading granulation of this is carried out with the liquid which dissolved hydroxyl propyl cellulose 20g in 400ml of water, and it dries at 50 degrees C for 4 hours. After carrying out the particle size regulation of this on the screen of 12 meshes, 8g of magnesium stearates could be added, and it mixed, and considered as the granule.

[0033] Example 102, suppositories [which make an active principle a 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane] 2, and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane 10g, and WITEPPUZORU RW-35 (Dinner Mill Nobel Chemicals, West Germany country) 90g may be taken, the

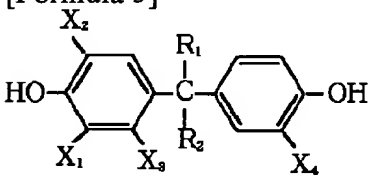
heating dissolution may be carried out at 60 degrees C, and it mixes. It slushed and cooled and this was made into suppositories so that it might become mold with per [piece / 1.5g or 3g] weight.

[0034] Example 112, injections [which make an active principle a 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane] 2, and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane 0.5g is taken, and it encloses with 5.0ml ampul of cotton seed oil, and considers as nonaqueous nature injections. The solution which added HCO-60 to the above-mentioned solution as injections for infusion solutions, and added 1.0g as a surfactant is prepared, and it is suspended and used for 200ml of 0.9% physiological salines at the time of use.

[0035] It measured according to the fibrin lump dissolution chronometric method of an example 12alpha2-PI activity inhibitory action plasmin inhibitor measuring method [Mutsumi Kazama, clinical pharmacology, and ** 27,215 (1976)]. Added 50micro of trial compound solutions l to Homo sapiens origin alpha2-PI(0.12mg/(ml))25microl, 25microl Added 4 casein units / Homo sapiens plasmin of ml after several minutes, the Homo sapiens fibrinogen solution and the thrombin solution were made to add and solidify so that the whole quantity may be further set to 500microl, and a fibrin lump's dissolution time amount was measured at the measurement temperature of 37 degrees C by the fibrin clot RISHISU time recorder (Fibrin Clot Lysis TimeRecorder: Toshiyasu business affairs). The difference of the plasmin activity of the sample under alpha2-PI un-living together and the plasmin activity of the sample under alpha2-PI existence was made into alpha2-PI activity, and it asked for the concentration of the trial compound which recovers 20% of the value (IC20), i.e., the plasmin activity which deactivated, from which a trial compound prevents this alpha2-PI activity 20%. A result is shown in Table 1 [Table 1] and [Table 2].

Table 1 [0036]

[Formula 3]



[0037]

[Table 1]

R_1	R_2	X_1	X_2	X_3	X_4	IC_{20} μM
CH_3	CH_3	CH_3	H	H	H	35
CH_3	CH_3	CH_3	H	H	CH_3	50
CH_3	CH_3	COOH	H	H	H	200
CH_3	CH_3	CH_3	CH_3	H	H	250
CH_3	CH_3	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	23
CH_3	CH_3	H	H	CH_3	H	90
CH_3	CH_3	H	H	$CH(CH_3)_2$	H	52

[0038]
[Table 2]
表1（続き）

R_1	R_2	X_1	X_2	X_3	X_4	IC_{20} μM
CH_3	$CH_2CH(CH_3)_2$	CH_3	H	H	CH_3	24
CH_3	$CH_2CH(CH_3)_2$	OH	H	H	H	19
CH_3	$CH_2CH(CH_3)_2$	OH	H	H	OH	23
CH_3	$CH_2CH(CH_3)_2$	COOH	H	H	COOH	230
CH_3	$CH_2CH(CH_3)_2$	NO_2	H	H	H	48
CH_3	$CH_2CH(CH_3)_2$	Cl	H	H	Cl	10

[0039]
[Effect of the Invention] The thrombolysis accelerator of this invention has the extremely excellent pharmacology effectiveness so that clearly from each above example.

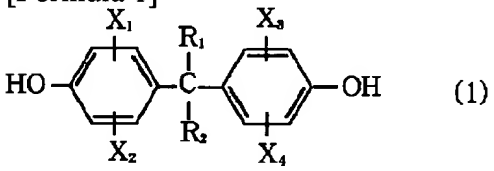
[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] a general formula -- (1 [-izing 1])
[Formula 1]



(1)

(The shape of a straight chain and branched-chain alkyl group of hydrogen or carbon numbers 1-10 is independently shown by the inside R1 and R2 of a formula.) X1, X2, X3, and X4 show hydrogen or a low-grade alkyl group, a nitro group, the amino group, an acetamide radical, hydroxyl, a low-grade alkanoyl radical, a hydroxymethyl group, a halogen atom, a lower alkoxy group, a carboxyl group, benzoyl, and an aryl group independently. However, X1, X2, X3, and X4 remove to coincidence the case where it is hydrogen. Thrombolysis accelerator which contains the salt permitted on the diphenyl hydrocarbon derivative expressed and its therapy as an active principle.
[Claim 2] R1 and R2 are a thrombolysis accelerator according to claim 1 which is hydrogen or the straight chain-like alkyl group of carbon numbers 1-10 independently.
[Claim 3] The thrombolysis accelerator according to claim 1 whose R2 R1 is the branched-chain alkyl group of carbon numbers 3-10 in hydrogen or the straight chain-like alkyl of carbon numbers 1-10.
[Claim 4] R1 and R2 are a thrombolysis accelerator according to claim 1 which is the branched-chain alkyl group of carbon numbers 3-10 independently.
[Claim 5] The thrombolysis accelerator which contains a 2 and 2-bis(4-hydroxy-3-methylphenyl)-4-methyl pentane as an active principle.
[Claim 6] The thrombolysis accelerator which contains a 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-pyrocatechol as an active principle.
[Claim 7] The thrombolysis accelerator which contains a 2 and 2-bis(3, 4-dihydroxy phenyl)-4-methyl pentane as an active principle.
[Claim 8] The thrombolysis accelerator which contains a 2 and 2-bis(3-chloro-4-hydroxyphenyl)-4-methyl pentane as an active principle.
[Claim 9] The thrombolysis accelerator which contains a 4-[1-(4-hydroxyphenyl)-1 and 3-dimethyl butylidene]-2-nitrophenol as an active principle.
[Claim 10] In a general formula (1) R1 by the straight chain-like ARUKI radical of carbon numbers 1-10 R2 is the branched-chain alkyl group of carbon numbers 3-10. Independently X1, X2, X3, and X4 Hydrogen or a low-grade alkyl group, A nitro group, the amino group, an acetamide radical, hydroxyl, a low-grade alkanoyl radical, a hydroxyl methyl group, a halogen atom, a lower alkoxy group, a carboxyl group, benzoyl, an aryl group (however, X1, X2, X3, and X4 remove to coincidence the case where it is hydrogen.)